

**The Case of Drug Causation of Childhood Asthma:
Paracetamol and Antibiotics**

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Tables 3 and 4

Table 3. Studies on the association between early antibiotic exposure and childhood asthma

Reference; number and age of children	Study details; outcome (asthma/wheezing)	Comments/Authors' conclusions
Cross-sectional Studies (ISAAC questionnaires, Beasley, 2008; involved no adjustment for respiratory infections)		
[1] 15,043; 5-7 and 9-11 years	Numbers of antibiotic courses during the first 3 years and of fever episodes during the first year of life associated with asthma and current wheeze at school age; risk of asthma diagnosis increased with early childhood infections	/ discussed various kinds of bias and were cautious to conclude a causative role of antibiotics
[2] 456; 5–10 years	Antibiotics associated with history of asthma or wheeze, but not with current wheeze; stronger association with use in the first year of life	/ considered a possible causal relationship
[3] 1,206; 6-7 years	Antibiotics during the first year of life weakly associated with asthma. Lower airway infections in early life were more prevalent in children who received antibiotics during first year of life; additional adjustment for history of severe respiratory infections during the first two years of life (assessed by questions) yielded no statistically significant interactions; hence adjustment eliminated from regression models	very weak association (OR1.7; CI 1.0-3.1) / concluded that antibiotics put those children at risk, who are genetically predisposed to atopic immune responses.
[4] 2443, 5-7, 8-10, and 11-14 years	Antibiotics associated with wheezing and diagnosis of asthma; contained retrospective substudy including 132 patients, where parents remembered indication of antibiotic use; here, the OR for asthma with antibiotic use in pulmonary indications was 14.6 (CI 4.2-51.0), but not significant in non-pulmonary indications (2.4; 0.3-22.5), the ORs for wheezing were 9.7 (5.3-17.7) in pulmonary and 3.9 (1.8-8.4) non-pulmonary indications.	The findings on association in non-pulmonary indications (asthma, loss; wheeze, weakening) suggest a role for respiratory infections / considered reverse causation the most likely possible explanation, but did not exclude true causation
[5] 1,492; 6-7 years; 3,000; 13-14 years	Antibiotics during the first year of life associated with wheeze; no association reported for age group 6-7 years; no association mentioned for the higher-age group	/ considered a possible causal relationship, but also acknowledged possibility of various types of bias
[6] 4,123; 6-7 years	Antibiotics associated with current wheezing and asthma in the first year of life	/ considered a possible causal relationship
[7], 26,400; 7 to 12 years	Antibiotics and episodes of fever associated with risk of asthma.	/ suggested an association with fever, antibiotics, and acute gastroenteritis during infancy
[8] 3,493; 6-7 years	Antibiotics in the first year of life associated with ever wheezing	/ sceptical about validity of association
[9] 4,606 Steiner school, 2,024 reference children; 5-13 years	Antibiotics in the first year of life or later associated with diagnosis of asthma and current wheezing	/ considered a possible causal relationship
[10] 8,470; 6-7 and 13-14 years	Antibiotics during infancy associated with recent wheezing (last 12 months)	weak association (OR 1.6, CI 1.1–2.1) / data listed, but not discussed
[11] 1,757; mean age 4 year;	Antibiotics in the previous 12 months associated with current wheezing (only in crude, not in adjusted OR)	no association in adjusted OR / no explicit discussion

Reference; number and age of children	Study details; outcome (asthma/wheezing)	Reference; number and age of Children
Still Cross-sectional Studies		
[12] 9,604; 6-7 years	3 Mexican cities found to share associations of antibiotics during the first year of life with wheezing ever and during previous year, wheezing in the last year and asthma ever	/ no special discussion
[13] 3,256; 6-7 years; 3,829; 13-14 years	Age 6-7 years: Antibiotics associated with current asthma symptoms	age 13-14 years: obviously no association / expressed concern about possible bias
[14]; 193,412; 6-7 years	Antibiotics in the first year of life associated with wheezing in the previous 12 months	/ considered a possible causal relationship
[15] 1,455; 6-7 years	Antibiotics in the first year of life associated with ever asthma	/ considered a possible causal relationship
[16] 10,873 6-7 years	Antibiotics in the first year of life associated with current wheeze	/ considered a possible causal relationship
[17] 834; median age 12, range 7–23 years	No significant association of use of antibiotics in neonates	Small number of cases; no statistical significance of association, only slight association in crude OR / considered a possible contribution of antibiotics to asthma in later life
[18] 4,554; mean age 9.5 years	Antibiotics during infancy for >3 days and history of bronchiolitis before 2 years of age associated with wheezing within 12 months at school age	/ considered a possible causal relationship
[19] 16,933; 6-7 years	Antibiotics in the first year of life strongly associated with transient early and persistent, weakly with late-onset wheezing (which further decreased upon more extensive adjustment); see Table 2 for paracetamol outcomes	/ concluded that the association, fully or in part, might be due to confounding.
[20] 2,170; 3-6 years	Antibiotics in the first year of life associated with asthma diagnosis; also associations with respiratory infections and antipyretics (addressed as mostly paracetamol, no quantification); strong temporal association with kindergarten entry	no adjustment reported; data consistent with confounding by indication / considered a possible causal relationship, but also recall bias

Reference; number and age of children	Study details	Outcome (asthma/wheezing)	Comments/Authors' conclusions
Case-control Studies, Nested in a Birth Cohort Study			
[21] 37 cases and 37 controls; mean age 4.4 years	Data from a prospective birth cohort; antibiotic exposure of children with recurrent wheeze and never wheeze; health-related diary cards during the first 3 years; review at 3 years and inclusion into case-control study; cases defined by sensitization and ≥ 3 reports of wheezy episodes; data from primary care records including antibiotic prescriptions and indications during first 3 years of life	More cases than controls received antibiotics during first three years of life; more cases than controls were prescribed antibiotics for lower respiratory tract infection during the first 3 years of life (not in the first year)	Association weak (OR 1.47, CI 1.01-2.13), low number of cases; reverse causation not excluded; studied age group does not allow firm conclusions on asthma / concluded that early life exposure to broad-spectrum antibiotics may be causative in expression of wheeze
[22] 745 cases, 833 controls (stage 2); until age of up to 10 years	Stage 1, 5,226 asthma cases, 104,520 controls; stage 2, questionnaire on risk factors including diagnosis of broncho-pulmonary disease	Antibiotics in the first year of life associated with asthma at both stages; previous broncho-pulmonary disease prior to index date showed strongest association with childhood asthma	"broncho-pulmonary disease" not further detailed, no mention of respiratory infections; 47 potential confounders considered, but no reference to broncho-pulmonary disease / discussed confounding by indication, recall bias, and reverse causation bias as possible confounders
Retrospective Birth Cohort Studies (Cases of interest identified after the incident)			
[23] 29,238; until 2.9 years (median) (range 0-11)	Administrative health data; extraction of incident diagnoses of asthma and wheeze; infections and prescriptions of antibiotics	Antibiotics associated with an increased risk of asthma; small effects, that could be explained to a large extent by consulting behaviour. Children with asthma more likely to have early respiratory tract infections (OR not adjusted).	heterogeneous age group, does not allow firm conclusions on asthma / saw no consistent evidence that antibiotics increase the risk of developing disease; considered that the association might be more in keeping with reverse than true causation.
[24] 746 adults, 19-46 years old	Parents of a representative birth cohort; antibiotic prescriptions and their indications in the first 5 years of life were collected from contemporary medical records and related to self-reports of asthma	Antibiotics in the first 5 years of life associated with later asthma; association was confined to lower respiratory infections and not observed in non-respiratory infections; no difference between antibiotic classes	single point survey, hence rather cross-sectional / considered reverse causation bias as the most plausible explanation

Reference; number and age of children	Study details	Outcome (asthma/wheezing)	Comments/Authors' conclusions
Still Retrospective Birth Cohort Studies (Cases of interest identified after the incident)			
[25] 13,116; until age of 7	Administrative health data; likelihood of asthma at age 7 years according to antibiotic prescriptions during first year of life	Antibiotics in the first year of life associated with asthma at 7 years; adjustment for lower respiratory infections reduced the association, restriction to children in an urban environment deleted it	Remaining association is weak (OR 1.05, CI 1.02–1.09); unexplained restriction to a rural environment, confounding by indication remains a possibility / concluded that early life antibiotics were a risk factor for the development of asthma at age 7
[26] 211,192; until age of up to 4 years	Administrative health data on dispensed prescriptions of antibiotics and asthma medication	Antibiotics associated with asthma medication; hazard ratios for typical airway antibiotics much stronger than for non-airway antibiotics; example first year: HR 2.27 (CI 2.17-2.37) vs. HR 1.04 (CI 0.78–1.40); at younger age, prescription of airway antibiotics more commonly preceded that of asthma medications; the reverse sequence was identified for non-airway medications.	Studied age group does not allow firm conclusions on asthma / concluded that association was caused by reverse causation or confounding by indication due to respiratory tract infections
Prospective Birth Cohort Studies (Cases of interest identified after recruitment)			
[27] 856; children from birth cohort available for an interview at age of 7 years	Three interviews (fourth day of life, home visit fifth post-natal week, telephone interview at median age of 85 days); interview at 7 years (expanded ISAAC questionnaire)	No association between antibiotic use in the first month of life and childhood asthma	cross-sectional information at 7 years, but more reliable analysis due to earlier sequence of questionnaires including question about chest infections / no association found
[28] 499 newborns with; 815 without risk factors; until age of 7 years	Newborn infants with and without risk factors for atopy, followed up at the age of 1, 3, 6, 12, and 18 months, and from then on at yearly intervals within 3 months of the child's birthday up to the age of 7 years; interview topics included asthmatic symptoms/diseases and drug history; diary of child's diseases; only antibiotic courses not related to the treatment of lower respiratory tract infections were included in statistical analysis	Repeated lower respiratory tract infections in the first 3 years of life associated with wheeze up to the age of 7 years; no association with antibiotics	/ found no effect of antibiotic treatment on asthma
[29] 448; until age of 5 years	Telephone questionnaire every 2 months, beginning at 2 months until age of 2, followed by interviews every 6 months. Questions about child's use of antibiotics including indication every 2 months during first year of life; asthma at 5 years defined by physician diagnosis plus ≥ 1 episode of wheezing in the past 12 months	Age 5 years: no association of asthma with antibiotics in first year of life (crude and adjusted ORs); persistent wheezing: crude OR for two or more courses of antibiotics, 1.9 (CI 0.9-3.9); OR adjusted for wheeze-associated respiratory illnesses, 0.6 (CI 0.2-1.5).	/ concluded that findings do not support association between antibiotic use in the first year of life and persistent wheezing or asthma at the age of 5

Reference; number and age of children	Study details	Outcome (asthma/wheezing)	Comments/Authors' conclusions
Still Prospective Birth Cohort Studies (Cases of interest identified after recruitment)			
[30] 4,408; until age of 5 years	Data derived from record systems for ambulatory care, dispensed pharmacy prescriptions, hospitalizations/visits to emergency departments. Starting at age 1 year, the presence of asthma (defined by ambulatory visits or hospitalizations for asthma, or by dispensing of typical asthma medications) was assessed annually.	Association of antibiotics in the first year of life with asthma persistent at age of 5 years; lost significance after adjustment for lower respiratory infections at all frequencies of antibiotic courses; e.g., ≥ 5 courses, crude OR 2.1, CI 1.5-3.2; adjusted OR 1.0, CI 0.7-1.4	/ concluded that findings do not support association between antibiotic use in early life and childhood asthma, but rather that frequent antibiotic use in early life is more common among asthmatic children.
[31] 642; until age of 8 years	Children seen annually until the age of 8 years. Reported infections and prescribed antibiotics by the age of 5 years were counted from physician records, including details on type of infection and indication of antibiotics; cross-sectional survey at 8 years on wheeze in the past 12 months using the ISAAC questionnaire	Antibiotic prescriptions for respiratory infection: weak associations with current wheeze in most age brackets; prescriptions for non- respiratory infections showed borderline associations in two age brackets only (0-5 years, OR 1.05, CI 1.00-1.10; 1-2 years, OR 1.18, CI 1.05-1.33), no association in age groups 0-1, 2-3, 3-4, 4-5 years	Discrepancy between respiratory and non-respiratory infections supports a role for the former in current wheeze / concluded there was no plausible causative relationship with subsequent respiratory allergies including wheeze
[32] 2,764; until age of 2 years	Questionnaires when infants were 3, 7, 12, and 24 months of age; questions including fever during the first 6 months and use of antibiotics; wheeze (7-, 12-, and 24-month questionnaires)	Association of antibiotics with recurrent wheeze; no adjustment for airway infections	studied age group does not allow firm conclusions on asthma; in a later overview, the same authors suggested confounding by indication (Kummeling and Thijs, 2008) / mechanistically, the authors considered use of antibiotics for viral infections with wheeze or interference of antibiotics with the commensal upper airway flora, paving the way for viral infections
[33] 526 (total study 871); until age of 7 years	Data collected at birth, 12 months, 3.5 years (question about current wheeze and use of antibiotics in first year of life) and 7 years (wheeze).	Association of antibiotics with current wheeze at 7, not 3.5 years; same pattern for association with day care	no details on adjustment, no information on indication for antibiotics / concluded that data support antibiotics as a risk factor, but also considered a role of respiratory infections including confounding by indication
[34] 16,682; until age of 12 months	Questionnaires: antibiotic treatment at neonatal age and during the first year of life; wheezing at 6 and 12 months	Antibiotics in neonatal ward and during first year of life associated with wheezing ever before 1 year (end of observation period)	studied age group does not allow firm conclusions on asthma; "wheezing ever" at 1 year is doubtful predictor of later asthma; reverse causation bias unlikely with neonate antibiotics; no adjustment for respiratory infections, confounding by indication still possible / concluded that antibiotics in the neonatal period are independent risk factors for wheezing

Reference; number and age of children	Study details	Outcome (asthma/wheezing)	Comments/Authors' conclusions
Still Prospective Birth Cohort Studies (Cases of interest identified after recruitment)			
[35] 108; until age of 5 years	Children at high genetic risk of atopy; daily diaries from day of birth on respiratory symptoms and medication use. Reporting symptoms prompted home visit and fortnightly follow-up telephone calls until resolution; annual history of doctor-diagnosed asthma and current wheeze was obtained by face-to-face interview.	Antibiotics in first year of life associated with doctor diagnosis of asthma, crude OR 2.3 (CI 1.2-4.5); OR adjusted to typical confounders, 1.5 (CI 0.7-3.2)	/ concluded that the data did not indicate that using antibiotics early in life led to asthma at 5 years.
[36] 154; until age of 12 months	Children recruited through maternity clinics; questionnaires mailed to parents when children reached ages of 3 weeks, and 6 and 12 months; wheezing assessed using ISAAC questionnaire	Antibiotics associated with wheezing during the first year of life; also: increasing total concentration of faecal anaerobic bacteria associated with wheezing	No information on indication for antibiotics / concluded from the lack of temporal associations that association between wheezing and antibiotics most likely reflected reverse causation.
[37] 986; until age of 4 years	Questionnaires at recruitment, and 3, 15, 24, 36 and 48 months of age; outcome measures from 15 months on; data on antibiotics collected at 3 and 15 months of age; inhaled medicines; presence/absence of chest infections; partly modified ISAAC questionnaires on wheeze and asthma; current asthma = asthma plus wheeze and/or inhaler use in the previous 12 months	Antibiotics before 3 months of life associated with asthma developing between birth and 15 months; crude OR 2.32 (CI 1.45-3.69); when adjusted for chest infections, OR = 1.58 (CI 0.96-2.60); no effect of antibiotics before 15 months on asthma developing after 15 months and present between 3 and 4 years	/ suggested that the effect of antibiotics on respiratory disease may be due to confounding by chest infections
[38] 251,817; until age of 2-9 years	Administrative health data; children exposed and not exposed to antibiotics in first 12 months of life recruited at 2 years and followed for up to 7 years; asthma diagnosis by hospital discharge for asthma, ICD9-coded medical service claims or 2 prescription for known asthma medications	Antibiotics in the first year of life associated with asthma	after excluding children with upper or lower respiratory infection the hazard ratio still showed a small association between antibiotics and asthma (but cf. Marra et al., 2011, below) / concluded that antibiotics pose a small risk
[39] 773; until age of 4 years	ISAAC questionnaires to collect environmental and health information including recurrent wheeze and medication, at the age of 1 year and then every 6 months until the age of 4 years	No positive association between antibiotics in first year of life and recurrent wheeze	The association was described as negative, i.e. a protective effect /

Reference; number and age of children	Study details	Outcome (asthma/wheezing)	Comments/Authors' conclusions
Still Prospective Birth Cohort Studies (Cases of interest identified after recruitment)			
[40] 3,306; until age of 8 years	Questions modified from ISAAC questionnaire; at 1 year, infections and antibiotic use; at 4 and 8 years, wheeze and asthma (defined as > 3 wheezes or ≥ 1 wheezing period with prescription for inhaled glucocorticoids in the past 12 months)	Association with antibiotics in first year: asthma at 8 years, crude OR 1.3 (CI 1.0-1.8); after adjustment for respiratory infections, OR 1.2 (CI 0.9-1.6)	confounding by indication revealed; also: reverse causation bias supported by subgroup analysis / concluded that the association could at least partially be explained by early respiratory infection.
[41] 1,401; until age of 6 years	Postpartum interview within 1 month of delivery; interviews at the child's sixth birthday (medical history, asthma diagnosis and symptoms, and medication use during the child's lifetime)	Antibiotics in the first 6 months of life associated with asthma at 6 years in children; no impact of lower airway infection in first year of life; no association in children with lower airway infection	recall bias possible (interview 6 years after birth); as discussed by [42] lack of distinction between persistent and late wheezers may still allow protopathic bias / concluded that antibiotic use was associated with asthma at 6 years of age, and that protopathic bias was unlikely to account for the main findings
[43] 424; until age of 5 years	Interviews on early illnesses and corresponding medication use at 2 weeks, 1 month, and 2, 3, 4, 6, and 9 months. Questionnaires at age 1, 2, 3, and 5 years on respiratory symptoms and diagnoses.	Antibiotics in the first 9 months of life associated with asthma by age 5. When analyses were adjusted for the number of illness visits in the first 9 months, the asthma-antibiotics relation was no longer significant.	/ concluded that at least a major portion of the association may be an artefact of the strong relation of illness visits to a doctor to both antibiotic use and risk for asthma diagnosis.
[44] 4,496; until age of 4.5 years	Questions at 6 and 12 months and 4.5 years of age, modified from ISAAC questionnaire	Antibiotics in the first week associated with enhanced risk of multiple-trigger and recurrent wheeze during the last 12 months at age of 4.5 years	Broad spectrum antibiotics were considered, no details; confounding by indication possible due to lack of information on infectious diagnosis / concluded that broad-spectrum antibiotics increased the risk of recurrent wheeze and multiple-trigger wheeze at preschool age.
[45] 310; until age of 5 years	Interviews every three months in the first 24 months after birth and every 6 months later; information on medical diagnosis of asthma, respiratory infections diagnosed by physician, and wheezing; use of antibiotics collected at 4 and 5 years, including specific name	Antibiotics in early childhood associated with asthma at age 5; when adjusted for respiratory infections, the OR lost statistical significance; macrolide and cephalosporin associations lost strength, but retained significance; no association with penicillins, with or without adjustment	/ considered that immuno-modulation might underlie asthma promotion by (certain) antibiotics

Reference; number and age of children	Study details	Outcome (asthma/wheezing)	Comments/Authors' conclusions
Still Prospective Birth Cohort Studies (Cases of interest identified after recruitment)			
[46] 9,640; children with asthma diagnosis; 96,496 children with no asthma at 6 years	as Marra et al., (2009); five groups defined by date of asthma diagnosis (2, 3, 4, 5 years and no asthma at 6 years); exclusion of index dates of < 2 years	Lower respiratory tract infections and bronchitis more frequently associated with antibiotics in the month before the index date of asthma diagnosis compared to the 5 months before; the opposite was true of upper respiratory tract infections, acute otitis media, lower urinary tract infection, and skin/soft tissue infection; dispensing rapidly decreased in the 6 months afterwards	/ considered that antibiotics were used for asthmatic wheeze (reverse causation) (based on the pattern of use of antibiotics and the immediate reduction in their use post-asthma diagnosis)

Table 4. Studies on the association between early paracetamol exposure and childhood asthma

Reference; number and age of children	Study details; outcome (asthma/wheezing)	Comments/Authors' conclusions
Cross-sectional Studies (ISAAC questionnaires, Beasley, 2008; involved no adjustment for respiratory infections)		
[6] 4,123; 6-7 years	Paracetamol in the first year of life associated with asthma; recent use at least once per month associated with current wheezing and asthma	/ considered a possible causal relationship
[8] 3,493; 6-7 years	Paracetamol in the first year of life associated with ever wheezing; frequent paracetamol in the last year increased the risk of wheezing	/ considered a possible causal relationship
[9] 4,606 Steiner school, 2,024 reference children; 5-13 years	Antipyretics in the first year of life associated with diagnosis of asthma; no association with later use	very slight association (OR 1.23, CI 1.01-1.51); studied antipyretics, with no distinction between individual drugs / favoured a causal relationship, which might be less pronounced in Steiner school children
[47] 6,000; 6-7 and 13-14 years	Children 6-7 years old: weak association of paracetamol in first year of life with ever wheezing; children 13-14 years old: association of paracetamol at least once a month with ever wheezing and wheezing in the last 12 months	where present, associations were borderline / considered a possible causal relationship
[48] 3,033; 13-14 yrs	Paracetamol in the past 12 months associated with current asthma	/ considered a possible causal relationship
[10] 8,470; 6-7 and 13-14 years	Paracetamol more than once a month associated with recent wheezing (last 12 months)	/ considered reverse causation and regarded evidence linking paracetamol use with asthma in children as minimal
[49] 3,026; 13-14 years	Paracetamol in the past 12 months associated with current wheeze and ever-diagnosed asthma	/ considered a possible causal relationship
[50] 3,089; 2-6 years	Frequent paracetamol associated with wheezing in the past 12 months	/ considered a possible causal relationship
[51] 205,487; 6-7 years	Use of paracetamol in the first year and current use associated with risk of asthma symptoms	relied on parents' recall of infant exposure after 6-7 years / considered a possible causal relationship
[11] 1,757; mean age 4 years	Use of paracetamol in the previous 12 months associated with current wheezing	/ no explicit conclusion
[12] 9,604; 6-7 years	3 Mexican cities found to share associations of wheezing ever with paracetamol during the first year of life and previous year; wheezing in the last year and asthma ever with paracetamol in the last year	/ considered a possible causal relationship
[52]; 17,683; age not indicated, probably 13-14 years	Use of paracetamol in the previous 12 months associated with current wheeze and asthma ever	association with asthma ever very slight (OR 1.16, CI 1.00-1.35) / considered a possible causal relationship

Reference; number and age of children	Study details; outcome (asthma/wheezing)		Comments/Authors' conclusions
Still Cross-sectional Studies (ISAAC questionnaires*)			
[13] 3,256, 6-7 years; 3,829, 13-14 years	Age 6-7 years: Use of paracetamol in the first year of life and the previous 12 months associated with current wheezing; age 13-14 years: Use of paracetamol in the previous 12 months associated with current wheezing		/ considered a possible causal relationship
[16] 10,873; 6-7 years	Paracetamol in the first year of life associated with current wheeze		/ considered a possible causal relationship
[53] 8334; 13-14 years	Paracetamol at least once per month in the past year associated with current wheezing		/ considered a possible causal relationship
[54] 322,959; 13-14 years;	Recent use of paracetamol associated with an increased risk of current wheeze		/ considered a possible causal relationship
[19] 16,933; 6-7 years	Paracetamol in the first year of life strongly associated with transient early and persistent, weakly with late-onset wheezing; the latter decreased upon more extensive adjustment (before adjustment, OR 1.18, CI 1.03-1.36); after adjustment, OR 1.12, CI 0.97-1.31); see table 1 for outcomes with antibiotics		/ concluded that the association might be, fully or in part, due to confounding.
[20] 2,170; 3-6 years	Antipyretics (addressed as mostly paracetamol, no quantification) in the first year of life (not in the previous year) associated with asthma diagnosis; also associations with antibiotics and respiratory infections; strong temporal association with kindergarten entry		no adjustment reported; data consistent with confounding by indication / considered a possible causal relationship, but also recall bias
[55] > 10,000 each group (6-7 and 13-14 years); (see comments)	In both age groups, paracetamol in the first year of life and paracetamol in the past 12 months associated with current asthma and wheezing ever		/ considered a possible causal relationship
Further Cross-sectional Studies, Case-control Design			
	Study details	Outcome (asthma/wheezing)	Comments/Authors' conclusions
[56] 84 pairs of siblings; 3-10 years	Association between paracetamol usage during the first 6 months of life, and childhood asthma; asthma patients as cases, healthy siblings as controls	Use of paracetamol between birth and 6 months of age, and between 4 and 6 months of age associated with non-allergic asthma (cases, 8/28; controls, 0/28); infection-related fever a more frequent indication in cases (30 vs. 17%)	small sample size / considered that part of the association might be due to reverse causation, confounding by indication and recall bias.
[57] 175 asthmatic children; 2-16 years	28 severe asthma cases and 147 non-severe asthmatic subjects were compared; questionnaires about symptom components of the Global Initiative for Asthma (primarily wheezing); risk factors according to the ISAAC questionnaires; diagnosis of current asthma by physician	Usual use of paracetamol for fever in the previous 12 months associated with severe asthma (not during first year of life)	no association in bivariate analysis; no adjustment for respiratory infections / considered a possible causal relationship, but cautioned against recall bias and reverse causation, that might especially distort the paracetamol data

Reference; number and age of children	Study details	Outcome (asthma/wheezing)	Comments/Authors' conclusions
Prospective Birth Cohort Studies (Cases of interest identified after recruitment)			
[58] 620; until age of 7 years	Paracetamol use prospectively documented on 18 occasions from birth to 2 years of age, followed until age of 7 years. Primary outcome, childhood asthma (questionnaire at 6 and 7 years); secondary outcome, infantile wheeze	Increasing frequency of paracetamol use weakly associated with increased risk of childhood asthma. After adjustment for frequency of respiratory infections, the association of paracetamol with asthma disappeared.	/ concluded that paracetamol use for non-respiratory causes was not associated with asthma
[59]; 3,097; until age of 7 years	Neonates enrolled; during the first year of life, parents used monthly diaries to record febrile episodes; respiratory, gastrointestinal, or urinary tract infections; and medication use, including antipyretics. At the ages of 6, 12, 18, and 24 months and annually from 2 to 6 years of age, parents were asked about a possible diagnosis of an allergic disease by a physician since the last follow-up.	Asthmatic children had more months with paracetamol and more months of prescriptions for respiratory tract infections, whereas the total number of febrile days or paracetamol treatment courses because of gastroenteritis or urinary tract infections did not differ between asthmatic and non-asthmatic children; children with asthma had 1.5 more febrile days and 1.27 more febrile days during respiratory tract infections than non-asthmatic children; similar trend in the number of months during the first year of life, during which children had at least one paracetamol course.	/ concluded that increased respiratory tract infection morbidity, not paracetamol use during infancy was associated with later development of asthma.
[60] > 7,000; until age of 7.5 years	Questions at 6 months after birth about paracetamol use in the infant and at age of 7.5 years; about wheezing and asthma in the past 12 months. Current asthma recognized by mother's report of a doctor's statement plus wheezing or asthma in the past 12 months.	Infant paracetamol use associated with childhood asthma was reduced by adjustment to borderline significance (OR 1.11, CI 1.00-1.23); association only detected in children who had wheezed in infancy (asthma in infancy wheezers, OR 1.44, CI 1.13-1.83; non-wheezers, OR 1.03, CI 0.92-1.16).	no adjustment for airway infections / considered as the most likely explanation that infants with a wheezing tendency are more likely to be given paracetamol for viral respiratory infections with fever.

Reference; number and age of children	Study details	Outcome (asthma/wheezing)	Comments/Authors' conclusions
Still Prospective Birth Cohort Studies			
[61] 757; until age of 3 years	Data collected from pregnancy to age 3; questionnaires about confounders at birth, 2 months, first and third birthday; symptoms of respiratory infection at 2 months and 1 year; about paracetamol in the last year, and (from ISAAC questionnaire) about wheeze-ever at age 1 and 3; incident wheeze defined by wheezing being reported at 3 years only, not at 1 year	Paracetamol in first year of life associated with wheeze; use associated with symptoms of respiratory infections in the first year of life; adjustment slightly reduced strength of association. Similar findings with recent use of paracetamol at age 3.	studied age group does not allow firm conclusions on asthma; reverse causation less likely as analysis was restricted to incident wheezers; adjustment for respiratory infections hinges on correct recall of symptoms, still leaving the possibility of confounding by indication and recall bias / suggested that frequent use of paracetamol early in life increases the risk of new-onset wheeze
[62] 1,016; outcomes at 10 years	Follow-up from a larger study on paracetamol in pregnancy; at 6 months, parents recorded all health events, medication use and health care contacts; infections including common airway infections and other febrile conditions; outcomes at 10 year follow-up (ISAAC questionnaire); asthma diagnosis required two of three factors (wheeze, doctor's diagnosis, asthma medication)	Crude data: No association between paracetamol use during the first 6 months and history of asthma or current wheeze; adjusting for gender yielded an association in girls, but not boys; no association with current wheeze/asthma, with and without adjustment	/ considered reverse causation a possibility because of paracetamol's association with history of, but not with current asthma
[63] 505; until age of 15 months; 914; 5-6 years	Children from a prospective birth cohort study; ISAAC questionnaires to determine paracetamol exposure between birth and 15 months and between 5 and 6 years; outcome data (reported current asthma, reported wheeze) at 6 years; adjustment for number of chest infections, but no data on the indication for paracetamol	Outcome at 6 years: no associations between early paracetamol use and asthma and wheeze; association between paracetamol use between 5 and 6 years (> 10 times) and asthma and wheeze; for less frequent use (3-10 times), association found for wheeze, not for asthma; adjustment (in a subgroup) for chest infections between 5 and 6 years weakened but did not dissipate the association	questionnaires from unequal groups are presented (full set at 5-6 years, a nested subset at 15 months); adjustment for chest infections did not cover the critical period of infancy and hence is not apt to dismiss a role for confounding by indication / considered a possible causal relationship, but also contributions by recall bias, reverse causation, and confounding by viral respiratory infections

Reference; number and age of children	Study details	Outcome (asthma/wheezing)	Comments/Authors' conclusions
Prospective Studies			
[64] 27,065; < 2 years	Febrile children randomized to receive paracetamol or ibuprofen (two dose levels); mailed questionnaire about hospitalization under a specific diagnosis during follow-up of 4 weeks	47% received antipyretic for respiratory infections; hospitalization for bronchiolitis/asthma rare; paracetamol = ibuprofen	very short study period; studied age group does not allow firm conclusions on asthma / concluded that antipyretic assignment was not associated with risk of hospitalization for asthma/ bronchiolitis
[65] 1,879; median age 46 months	Children with febrile illness randomly assigned to paracetamol or ibuprofen (two dose levels); after 4 weeks, identification of children with a recent asthma history (hospitalizations, medical records, discharge diagnoses). Asthma morbidity defined by a report of hospitalization or outpatient visit for asthma and restricted to children receiving typical asthma medication.	hospitalization for asthma: paracetamol = ibuprofen; outpatient visits for asthma: paracetamol > ibuprofen if antipyretic treatment was for respiratory infections; paracetamol = ibuprofen for other causes of fever	no placebo; very short study period; studied age group does not allow firm conclusions on asthma; for paracetamol to be an independent risk factor of asthma, paracetamol > ibuprofen would be expected with any cause of antipyretic treatment / concluded that the observed difference might be attributable to increased risk after paracetamol or a decrease after ibuprofen

References

1. von Mutius E, Illi S, Hirsch T, Leupold W, Keil U et al. (1999) Frequency of infections and risk of asthma, atopy and airway hyperresponsiveness in children. *Eur Respir J* 14 (1):4-11
2. Wickens K, Pearce N, Crane J, Beasley R (1999) Antibiotic use in early childhood and the development of asthma. *Clin Exp Allergy* 29 (6):766-771
3. Droste JH, Wieringa MH, Weyler JJ, Nelen VJ, Vermeire PA et al. (2000) Does the use of antibiotics in early childhood increase the risk of asthma and allergic disease? *Clin Exp Allergy* 30 (11):1547-1553
4. Wjst M, Hoelscher B, Frye C, Wichmann HE, Dold S et al. (2001) Early antibiotic treatment and later asthma. *Eur J Med Res* 6 (6):263-271
5. Awasthi S, Kalra E, Roy S (2004) Prevalence and risk factors of asthma and wheeze in school-going children in Lucknow, North India. *Indian Pediatr* 41 (12):1205-1210
6. Cohet C, Cheng S, MacDonald C, Baker M, Foliaki S et al. (2004) Infections, medication use, and the prevalence of symptoms of asthma, rhinitis, and eczema in childhood. *J Epidemiol Community Health* 58 (10):852-857. doi:58/10/852 [pii] 10.1136/jech.2003.019182
7. Ahn KM, Lee MS, Hong SJ, Lim DH, Ahn YM et al. (2005) Fever, use of antibiotics, and acute gastroenteritis during infancy as risk factors for the development of asthma in Korean school-age children. *J Asthma* 42 (9):745-750. doi:10.1080/02770900500308023
8. Barragan-Mejueiro MM, Morfin-Maciél B, Nava-Ocampo AA (2006) A Mexican population-based study on exposure to paracetamol and the risk of wheezing, rhinitis, and eczema in childhood. *J Investig Allergol Clin Immunol* 16 (4):247-252
9. Floistrup H, Swartz J, Bergstrom A, Alm JS, Scheynius A et al. (2006) Allergic disease and sensitization in Steiner school children. *J Allergy Clin Immunol* 117 (1):59-66. doi:10.1016/j.jaci.2005.09.039
10. Sharma SK, Banga A (2007) Prevalence and risk factors for wheezing in children from rural areas of north India. *Allergy Asthma Proc* 28 (6):647-653. doi:10.2500/aap.2007.28.3059
11. Castro-Rodriguez JA, Garcia-Marcos L, Alfonseda Rojas JD, Valverde-Molina J, Sanchez-Solis M (2008) Mediterranean diet as a protective factor for wheezing in preschool children. *J Pediatr* 152 (6):823-828, 828 e821-822. doi:10.1016/j.jpeds.2008.01.003
12. Del-Rio-Navarro BE, Ito-Tsuchiya FM, Berber A, Zepeda-Ortega B, Sienra-Monge JJ et al. (2008) Study of the relationship between acetaminophen and asthma in Mexican children aged 6 to 7 years in 3 Mexican cities using ISAAC methodology. *J Investig Allergol Clin Immunol* 18 (3):194-201

13. Garcia E, Aristizabal G, Vasquez C, Rodriguez-Martinez CE, Sarmiento OL et al. (2008) Prevalence of and factors associated with current asthma symptoms in school children aged 6-7 and 13-14 yr old in Bogota, Colombia. *Pediatr Allergy Immunol* 19 (4):307-314. doi:10.1111/j.1399-3038.2007.00650.x
14. Foliaki S, Pearce N, Bjorksten B, Mallol J, Montefort S et al. (2009) Antibiotic use in infancy and symptoms of asthma, rhinoconjunctivitis, and eczema in children 6 and 7 years old: International Study of Asthma and Allergies in Childhood Phase III. *J Allergy Clin Immunol* 124 (5):982-989. doi:10.1016/j.jaci.2009.08.017
15. Karimi M, Mirzaei M (2009) Antibiotic use and symptoms of asthma, allergic rhinitis, and eczema in children. *Iran J Pediatr* 19 (2):141-146
16. Mitchell EA, Stewart AW, Clayton T, Asher MI, Ellwood P et al. (2009) Cross-sectional survey of risk factors for asthma in 6-7-year-old children in New Zealand: International Study of Asthma and Allergy in Childhood Phase Three. *J Paediatr Child Health* 45 (6):375-383. doi:10.1111/j.1440-1754.2009.01504.x
17. Sobko T, Schiött J, Ehlin A, Lundberg J, Montgomery S et al. (2010) Neonatal sepsis, antibiotic therapy and later risk of asthma and allergy. *Paediatr Perinat Epidemiol* 24 (1):88-92
18. Kwon SJ, Lee CW (1998) Figurate purpuric eruptions on the trunk: acetaminophen-induced rashes. *J Dermatol* 25 (11):756-758
19. Rusconi F, Gagliardi L, Galassi C, Forastiere F, Brunetti L et al. (2011) Paracetamol and antibiotics in childhood and subsequent development of wheezing/asthma: association or causation? *Int J Epidemiol* 40 (3):662-667. doi:10.1093/ije/dyq263
20. Yeh KW, Ou LS, Yao TC, Chen LC, Lee WI et al. (2011) Prevalence and risk factors for early presentation of asthma among preschool children in Taiwan. *Asian Pac J Allergy Immunol* 29 (2):120-126
21. Thomas M, Custovic A, Woodcock A, Morris J, Simpson A et al. (2006) Atopic wheezing and early life antibiotic exposure: a nested case-control study. *Pediatr Allergy Immunol* 17 (3):184-188. doi:PAI389 [pii] 10.1111/j.1399-3038.2006.00389.x
22. Martel MJ, Rey E, Malo JL, Perreault S, Beauchesne MF et al. (2009) Determinants of the incidence of childhood asthma: a two-stage case-control study. *Am J Epidemiol* 169 (2):195-205. doi:10.1093/aje/kwn309
23. McKeever TM, Lewis SA, Smith C, Collins J, Heatlie H et al. (2002b) Early exposure to infections and antibiotics and the incidence of allergic disease: a birth cohort study with the West Midlands General Practice Research Database. *J Allergy Clin Immunol* 109 (1):43-50
24. Cullinan P, Harris J, Mills P, Moffat S, White C et al. (2004) Early prescriptions of antibiotics and the risk of allergic disease in adults: a cohort study. *Thorax* 59 (1):11-15
25. Kozyrskyj AL, Ernst P, Becker AB (2007) Increased risk of childhood asthma from antibiotic use in early life. *Chest* 131 (6):1753-1759. doi:10.1378/chest.06-3008

26. Almqvist C, Wettermark B, Hedlin G, Ye W, Lundholm C (2012) Antibiotics and asthma medication in a large register-based cohort study - confounding, cause and effect. *Clin Exp Allergy* 42 (1):104-111. doi:10.1111/j.1365-2222.2011.03850.x
27. Ponsonby AL, Couper D, Dwyer T, Carmichael A, Kemp A (1999) Relationship between early life respiratory illness, family size over time, and the development of asthma and hay fever: a seven year follow up study. *Thorax* 54 (8):664-669
28. Illi S, von Mutius E, Lau S, Bergmann R, Niggemann B et al. (2001) Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. *BMJ* 322 (7283):390-395
29. Celedon JC, Litonjua AA, Ryan L, Weiss ST, Gold DR (2002) Lack of association between antibiotic use in the first year of life and asthma, allergic rhinitis, or eczema at age 5 years. *Am J Respir Crit Care Med* 166 (1):72-75
30. Celedon JC, Fuhlbrigge A, Rifas-Shiman S, Weiss ST, Finkelstein JA (2004) Antibiotic use in the first year of life and asthma in early childhood. *Clin Exp Allergy* 34 (7):1011-1016. doi:10.1111/j.1365-2222.2004.01994.x
31. Harris JM, Mills P, White C, Moffat S, Newman Taylor AJ et al. (2007) Recorded infections and antibiotics in early life: associations with allergy in UK children and their parents. *Thorax* 62 (7):631-637. doi:thx.2006.072124 [pii] 10.1136/thx.2006.072124
32. Kummeling I, Stelma FF, Dagnelie PC, Snijders BE, Penders J et al. (2007) Early life exposure to antibiotics and the subsequent development of eczema, wheeze, and allergic sensitization in the first 2 years of life: the KOALA Birth Cohort Study. *Pediatrics* 119 (1):e225-231. doi:10.1542/peds.2006-0896
33. Mitchell EA, Robinson E, Black PN, Becroft DM, Clark PM et al. (2007) Risk factors for asthma at 3.5 and 7 years of age. *Clin Exp Allergy* 37 (12):1747-1755. doi:CEA2847 [pii] 10.1111/j.1365-2222.2007.02847.x [doi]
34. Alm B, Erdes L, Mollborg P, Pettersson R, Norvenius SG et al. (2008) Neonatal antibiotic treatment is a risk factor for early wheezing. *Pediatrics* 121 (4):697-702. doi:10.1542/peds.2007-1232
35. Kusel MM, de Klerk N, Holt PG, Sly PD (2008) Antibiotic use in the first year of life and risk of atopic disease in early childhood. *Clin Exp Allergy* 38 (12):1921-1928. doi:10.1111/j.1365-2222.2008.03138.x
36. Verhulst SL, Vael C, Beunckens C, Nelen V, Goossens H et al. (2008) A longitudinal analysis on the association between antibiotic use, intestinal microflora, and wheezing during the first year of life. *J Asthma* 45 (9):828-832. doi:10.1080/02770900802339734
37. Wickens K, Ingham T, Epton M, Pattemore P, Town I et al. (2008) The association of early life exposure to antibiotics and the development of asthma, eczema and atopy in a birth

- cohort: confounding or causality? *Clin Exp Allergy* 38 (8):1318-1324. doi:10.1111/j.1365-2222.2008.03024.x
38. Marra F, Marra CA, Richardson K, Lynd LD, Kozyrskyj A et al. (2009) Antibiotic use in children is associated with increased risk of asthma. *Pediatrics* 123 (3):1003-1010. doi:123/3/1003 [pii] 10.1542/peds.2008-1146
 39. Dom S, Droste JH, Sariachvili MA, Hagendorens MM, Oostveen E et al. (2010) Pre- and post-natal exposure to antibiotics and the development of eczema, recurrent wheezing and atopic sensitization in children up to the age of 4 years. *Clin Exp Allergy* 40 (9):1378-1387. doi:10.1111/j.1365-2222.2010.03538.x
 40. Mai XM, Kull I, Wickman M, Bergstrom A (2010) Antibiotic use in early life and development of allergic diseases: respiratory infection as the explanation. *Clin Exp Allergy* 40 (8):1230-1237. doi:10.1111/j.1365-2222.2010.03532.x
 41. Risnes KR, Belanger K, Murk W, Bracken MB (2011) Antibiotic exposure by 6 months and asthma and allergy at 6 years: Findings in a cohort of 1,401 US children. *Am J Epidemiol* 173 (3):310-318. doi:10.1093/aje/kwq400
 42. Gagliardi L, Rusconi F, Galassi C, Forastiere F (2011) Re.: "Antibiotic exposure by 6 months and asthma and allergy at 6 years: findings in a cohort of 1,401 US children". *Am J Epidemiol* 173 (11):1343; author reply 1344-1345. doi:10.1093/aje/kwr082
 43. Su Y, Rothers J, Stern DA, Halonen M, Wright AL (2010) Relation of early antibiotic use to childhood asthma: confounding by indication? *Clin Exp Allergy* 40 (8):1222-1229. doi:10.1111/j.1365-2222.2010.03539.x
 44. Goksor E, Alm B, Thengilsdottir H, Pettersson R, Aberg N et al. (2011) Preschool wheeze - impact of early fish introduction and neonatal antibiotics. *Acta Paediatr* 100 (12):1561-1566. doi:10.1111/j.1651-2227.2011.02411.x
 45. Jedrychowski W, Perera F, Mauger U, Mroz E, Flak E et al. (2011) Wheezing and asthma may be enhanced by broad spectrum antibiotics used in early childhood. Concept and results of a pharmacoepidemiology study. *J Physiol Pharmacol* 62 (2):189-195
 46. Marra F, Marra CA, Richardson K, Lynd LD, Fitzgerald MJ (2011) Antibiotic consumption in children prior to diagnosis of asthma. *BMC Pulm Med* 11:32. doi:10.1186/1471-2466-11-32
 47. Karimi M, Mirzaei M, Ahmadi MH (2006) Acetaminophen use and the symptoms of asthma, allergic rhinitis and eczema in children. *Iran J Allergy Asthma Immunol* 5 (2):63-67. doi:05.01/ijaa.6367
 48. Kuschner FC, Alves da Cunha AJ (2007) Environmental and socio-demographic factors associated to asthma in adolescents in Rio de Janeiro, Brazil. *Pediatr Allergy Immunol* 18 (2):142-148. doi:10.1111/j.1399-3038.2006.00477.x
 49. Vlaski E, Stavric K, Isjanovska R, Seckova L, Kimovska M (2007) Acetaminophen intake and risk of asthma, hay fever and eczema in early adolescence. *Iran J Allergy Asthma Immunol* 6 (3):143-149. doi:06.03/ijaa.143149

50. Wong GW, Leung TF, Ma Y, Liu EK, Yung E et al. (2007) Symptoms of asthma and atopic disorders in preschool children: prevalence and risk factors. *Clin Exp Allergy* 37 (2):174-179. doi:10.1111/j.1365-2222.2007.02649.x
51. Beasley R, Clayton T, Crane J, von Mutius E, Lai CK et al. (2008) Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6-7 years: analysis from Phase Three of the ISAAC programme. *Lancet* 372 (9643):1039-1048. doi:S0140-6736(08)61445-2 [pii] 10.1016/S0140-6736(08)61445-2 [doi]
52. Foliaki S, Annesi-Maesano I, Tuuau-Potoi N, Waqatakirewa L, Cheng S et al. (2008) Risk factors for symptoms of childhood asthma, allergic rhinoconjunctivitis and eczema in the Pacific: an ISAAC Phase III study. *Int J Tuberc Lung Dis* 12 (7):799-806
53. Wang HY, Pizzichini MM, Becker AB, Duncan JM, Ferguson AC et al. (2010) Disparate geographic prevalences of asthma, allergic rhinoconjunctivitis and atopic eczema among adolescents in five Canadian cities. *Pediatr Allergy Immunol* 21 (5):867-877. doi:10.1111/j.1399-3038.2010.01064.x
54. Beasley RW, Clayton TO, Crane J, Lai CK, Montefort SR et al. (2011) Acetaminophen use and risk of asthma, rhinoconjunctivitis, and eczema in adolescents: International Study of Asthma and Allergies in Childhood Phase Three. *Am J Respir Crit Care Med* 183 (2):171-178. doi:10.1164/rccm.201005-0757OC
55. Gonzalez-Barcala FJ, Pertega S, Castro TP, Sampedro M, Lastres JS et al. (2012) Exposure to paracetamol and asthma symptoms. *Eur J Public Health*. doi:cks061 [pii] 10.1093/eurpub/cks061
56. Koniman R, Chan YH, Tan TN, Van Bever HP (2007) A matched patient-sibling study on the usage of paracetamol and the subsequent development of allergy and asthma. *Pediatr Allergy Immunol* 18 (2):128-134. doi:PAI484 [pii] 10.1111/j.1399-3038.2006.00484.x
57. Rodriguez Martinez C, Sossa M, Goss CH (2008) Factors associated with severe disease in a population of asthmatic children of Bogota, Colombia. *J Asthma* 45 (2):141-147. doi:791553941 [pii] 10.1080/02770900701840253 [doi]
58. Lowe AJ, Carlin JB, Bennett CM, Hosking CS, Allen KJ et al. (2010) Paracetamol use in early life and asthma: prospective birth cohort study. *BMJ* 341:c4616. doi:10.1136/bmj.c4616
59. Schnabel E, Heinrich J, Group LS (2010) Respiratory tract infections and not paracetamol medication during infancy are associated with asthma development in childhood. *J Allergy Clin Immunol* 126 (5):1071-1073. doi:10.1016/j.jaci.2010.08.023
60. Shaheen SO, Newson RB, Ring SM, Rose-Zerilli MJ, Holloway JW et al. (2010) Prenatal and infant acetaminophen exposure, antioxidant gene polymorphisms, and childhood asthma. *J Allergy Clin Immunol* 126 (6):1141-1148 e1147. doi:10.1016/j.jaci.2010.08.047

61. Amberbir A, Medhin G, Alem A, Britton J, Davey G et al. (2011) The role of acetaminophen and geohelminth infection on the incidence of wheeze and eczema: a longitudinal birth-cohort study. *Am J Respir Crit Care Med* 183 (2):165-170. doi:201006-0989OC [pii] 10.1164/rccm.201006-0989OC
62. Bakkeheim E, Mowinckel P, Carlsen KH, Haland G, Carlsen KC (2011) Paracetamol in early infancy: the risk of childhood allergy and asthma. *Acta Paediatr* 100 (1):90-96. doi:10.1111/j.1651-2227.2010.01942.x
63. Wickens K, Beasley R, Town I, Epton M, Pattemore P et al. (2011) The effects of early and late paracetamol exposure on asthma and atopy: a birth cohort. *Clin Exp Allergy* 41 (3):399-406. doi:10.1111/j.1365-2222.2010.03610.x
64. Lesko SM, Mitchell AA (1999) The safety of acetaminophen and ibuprofen among children younger than two years old. *Pediatrics* 104 (4):e39
65. Lesko SM, Louik C, Vezina RM, Mitchell AA (2002) Asthma morbidity after the short-term use of ibuprofen in children. *Pediatrics* 109 (2):E20